## REMARKS

The sole issue in this case is whether claims 59-61, 79, and 108-118 are obvious over Campochiaro et al. (USP 5,824,685) in view of Oikawa et al.

The examiner argues that (1) Campochiaro teaches use of the claimed retinoids of formula V for treating proliferative retinopathy, (2) Oikawa teaches use of formula I retinoids for treating non-proliferative diabetic retinopathy[1], hence (3), it would have been obvious to use Campochiaro's formula V retinoids for treatment of non-proliferative diabetic, retinopathy.

We traverse. At the outset, we note that the main claim (59) is now limited to fenretinide, which is within the scope of the prior generic formula V.

In our view, it would not have been obvious to one of ordinary skill in the art to use fenretinide for treatment of non-proliferative diabetic retinopathy or macular edema in view of the cited documents. The compounds and medical indications mentioned in Campochiaro et al. and Oikawa et al. are completely different from fenretinide and non-proliferative diabetic retinopathy/ macular edema.

**1. Different medical indications:**

The present invention relates to the prevention / treatment of non-proliferative diabetic retinopathy and/ or macular edema. These conditions are caused by a retinal neuroinflammatory response to diabetes and characterized by the following:

Mild to Severe non-proliferative diabetic retinopathy: (Also called background retinopathy). The earliest signs of

[1] We have previously questioned this interpretation of Oikawa, see page 13 of our amendment of November 30, 2010, and our opinion on this point has not changed.

this condition, detectable only by invasive histopathological studies that cannot be made in live human patients, are inflammatory changes in the neuronal and glial cells of the retina, such as upregulation of glial acidic fibrillary protein. At the earliest stage that can be seen in humans by ophthalmoscopy, microaneurysms occur. They are small out-pouchings of the retinal capillaries. This is accompanied by leakage from retinal vessels that may lead to edema of the center of the macula and precipitation of extracellular lipoprotein (hard exudate) and reduced visual acuity.

Macular edema: Occurs when fluid and protein deposits collect in or under the macula of the eye. The swelling may distort a person's central vision, as the macula is near the centre of the retina at the back of the eyeball. This area holds tightly packed cones that provide sharp, clear central vision to enable a person to see form, color, and detail that is directly in the line of sight.

Campochiaro discloses the use of retinoic acid receptor (RAR) agonists for use in treatment of proliferative vitreoretinopathy (PVR) (abstract), which is a condition occurring after surgery or trauma (column 3 lines 49-50) and associated with retinal wound repair (column 4, line 30-32). Thus, PVR is a condition that arises after spontaneous or traumatic hole formation in the retina with subsequent detachment of the retina. PVR is independent of diabetes and distinct from diabetic retinopathy in that PVR involves proliferation of retinal pigment epithelium cells that have been transformed to have fibroblast characteristics whereas proliferative diabetic retinopathy involves proliferation of endothelial and angioblastic cells that form blood vessels.

A condition involving proliferation and detachment of the retina caused by surgery or trauma is completely different

from a neuroinflammatory disease caused by diabetes. Proliferative vitreoretinopathy is an independent disease entity which is described separately from diabetic retinopathy in reference textbooks and original science communications. Thus Campochiaro et al. is viewed as irrelevant for a skilled person studying diabetic neuroinflammatory conditions.

Oikawa et al. only suggests that Re 80, Am 580 and Am 80 can be used for treatment of angiogenesis-dependent diabetic retinopathy which is a sort of diabetic retinopathy characterized by the formation of new blood vessels between the retina and the vitreous body. The present invention relates to non-proliferative diabetic retinopathy and macular edema, which by definition do not involve angiogenesis (see above). Macular edema is a frequent manifestation of non-proliferative diabetic retinopathy and patients can develop legal blindness without having proliferative diabetic retinopathy. Hence it can be seen that clinically meaningful progression of disease does not depend upon the development of angiogenesis. Proliferative diabetic retinopathy is not generally accompanied by macular edema. However, patients suffering from proliferative diabetic retinopathy can also develop macular edema.

Further, Oikawa et al. discloses that Re 80, Am580 and Am 80 have an inhibitory effect on embryogenic angiogenesis in chickens (fig. 1). The model applied by Oikawa et al. consists of a fertilized egg wherein formation of vessels on the chick chorioallantoic membrane is examined. Because there are no functioning neurons in relation to these vessels, the model offers no opportunity of studying the driving force of the retinal neurons on retinal vascular pathology. Hence the model is exclusively a model of angiogenesis outside the central nervous system (of which the retina is a part), and

the skilled person would find such a model irrelevant for studying a neuroinflammatory response and non-proliferative diabetic retinopathy.

In conclusion, a person skilled in the art would not find Oikawa et al. relevant, since the medical indications of the present invention are fundamentally different from the conditions mentioned in Oikawa et al.

**2. Different compounds:**

Amended claim 59 only covers fenretinide. The compound is not suggested nor disclosed in any of the cited prior art documents.

2.1. Structure

Oikawa alludes to prior studies by his group relating to

* retinoic acid

*the synthetic retinoid Ch 55

((E)-4[3-(3,5-di-tert-butyl-phenyl)-3-oxo-1-propenyl] benzoic acid

*1α, 25-dihyhydroxyvitamin $D_3$

*22-oxa-1,25-dihydroxyvitamin $D_3$

Oikawa also discloses three new synthetic retinoids, Re80, Am580, and Am80 (Fig. 1(A)).

In asserting that the Oikawa reference "makes clear that the genus of compounds of formula V have been previously used for the treatment of diabetic retinopathy, we assume that the examiner was thinking of retinoic acid.

The following table compares the required formula V substituents for fenretinide and retinoic acid, respectively.

| | fenretinide | retinoic acid |
|---|---|---|
| R11 | CONH-4-hydroxyphenyl | COOH |
| R12 | $CH_3$ | $CH_3$ |
| R1 | $CH_3$ | $CH_3$ |
| R3 | H | H |
| R4 | $CH_3$ | $CH_3$ |
| R5 | H | H |
| R6 | H | H |
| R7 | H | H |
| R8 | H | H |
| R9 | $CH_3$ | $CH_3$ |
| R10 | $CH_3$ | $CH_3$ |
| config | all trans (E) | all trans (E) |

It can be seen that there is a substantial change at the R11 position.

The three new synthetic retinoids are much less similar to fenretinide than was retinoic acid, i.e., Oikawa moved further away from the fenretinide structure. The differences are so many that it is difficult to enumerate them.

Referring to formula V, on the left hand side, there is a six-membered carbon ring with a single double bond. In fenretinide one of these carbons bears two methyl substituents (R9, R10).

In contrast, the Oikawa retinoids have a six membered ring with four saturated carbons fused to an aromatic ring, and two of the saturated carbons each bear two methyl substituents (cp. R5, R6, R9, R10).

On the right hand side, in fenretinide, we have R', which is 4-hydroxyphenyl, whereas the Oikawa retinoids have Ph-COOH.

In-between, the structures are quite different. In fenretinide, we have the structure

$-CH=CH-C(CH_3)=CH-CH=CH-\ C(CH_3)=CH-CONH-$,

whereas for Oikawa Re80 we have,

$-CO-CH=CH(OH)-$,

for Am 580,

$-CO-NH-$

and for Am 80

$-NH-CO-$.

Referring to Campochiaro table 3, the first compound shown in retinoic acid, and the second is a stereoisomer thereof.

Campochiaro compounds 521, 121, 509, 183, 659, 867, and 870 are all further removed from fenretinide than is retinoic acid, itself. The structural changes are as pervasive as for the Oikawa retinoids, and we see no need to enumerate them, too, as they are equally apparent.

Thus, both Oikawa and Campochiaro teach, by synthetic example, away from fenretinide.

2.2. Function

The compounds mentioned in Oikawa et al. and Campochiaro et al. function by other mechanisms than fenretinide:

Proliferative diabetic retinopathy occurs when retinal blood vessels react to a biochemical distress signal by activating angiogenesis. Non-proliferative diabetic retinopathy and macular edema are primary neuroglial disorders with inflammatory characteristics. There is a remarkable difference, since the compounds mentioned by Oikawa et al. are mentioned as capable of suppressing an angiogenic response of the blood vessels, while the present invention provides a compound which functions on the retinal neurons to decrease metabolic demands.

The three synthetic retinoids tested by Oikawa et al. all have affinity for the retinoid nuclear receptors (RAR and RXR) which are found in a variety of tissues of the body. Further, the compounds disclosed by Campochiaro et al. are defined as "RAR agonists, preferably one with specific activity for the retinoic acid receptors" (abstract). Specifically, these substances which are nuclear receptors agonists must be expected to have unspecific and clinically undesirable antiangiogenic effects in multiple organ systems, in wound healing etc.

Fenretinide, on the other hand has little or no affinity for these receptors. Fenretinide has been found by the inventor to have the ability to reduce metabolic demand in the retina by reversibly inhibiting the function of the rod photoreceptors. At the same time, the patient is spared of adverse effects outside the retina that are mediated by the RAR/RXR receptors. Fenretinide is thus capable of preventing non-proliferative diabetic retinopathy and macular edema in a reversible and more specific manner than the state-of-the-art method of irreversibly destroying photoreceptors by retinal laser photocoagulation. This is a considerable improvement.

Respectfully submitted,

BROWDY AND NEIMARK, P.L.L.C.
Attorneys for Applicant(s)

By: _____
Iver P. Cooper
Registration No. 28,005

IPC:lms
Telephone No.: (202) 628-5197
Facsimile No.: (202) 737-3528
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